MEDICINE LABORATORY

GDAŃSKI UNIWERSYTET MEDYCZNY

UPPSALA UNIVERSITET

3PLAB: Advancing Basic and Clinical Research to Unravel the Role of Post-Zygotic Mutations for Age-Related Diseases

Jan Dumanski, Arkadiusz Piotrowski, Jakub Mieczkowski, Natalia Filipowicz

European Funds Smart Growth

Republic of Poland

FNP Foundation for Polish Science

European Union European Regional Development Fund

3P-Medicine Laboratory at Medical University of Gdańsk

GDAŃSKI UNIWERSYTET MEDYCZNY

3P = Preventive, Personalized, Precision

Project: Mutations acquired during lifetime that lead to increased risk for human disease, with focus on cancer

GROUP 1: Loss of chromosome Y and disease

PI: Jan Dumanski

GROUP 2: Mosaicism for autosomal post-zygotic mutations (PZMs)

PI: Arkadiusz Piotrowski

GROUP 3: Computational Biology - Chromatin structures reflecting cellular states

PI: Jakub Mieczkowski

Biobank for PZM studies

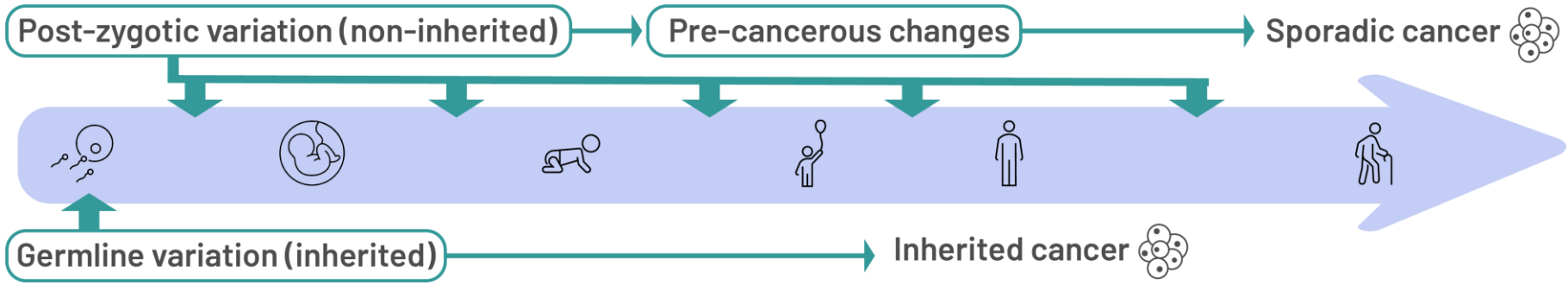
Coordinator: Natalia Filipowicz

Post-zygotic mutations and aging-related diseases

GDAŃSKI UNIWERSYTET MEDYCZNY

With a diploid genome size of 6 x 10^9 nucleotides and ~10^{13} cells per soma, the body of a middle-aged human might contain *>10^{16} base substitutions*

~10% of these changes can have adverse functional effects, of which some lead to disease



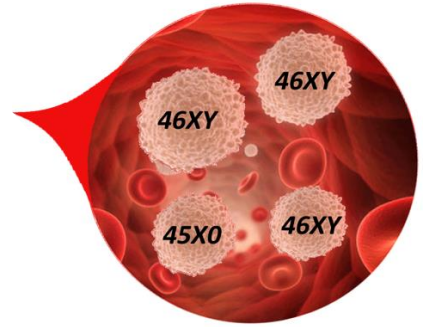
NIH National Institutes of Health
Office of Strategic Coordination–The Common Fund

MaHT Somatic Mosaicism across Human Tissues

$140 million funding/ 5 years

LOY is the most common post-zygotic mutation

GDAŃSKI UNIWERSYTET MEDYCZNY



LETTERS

nature genetics

LOY = Loss of Y

Mosaic loss of chromosome Y in peripheral blood is associated with shorter survival and higher risk of cancer

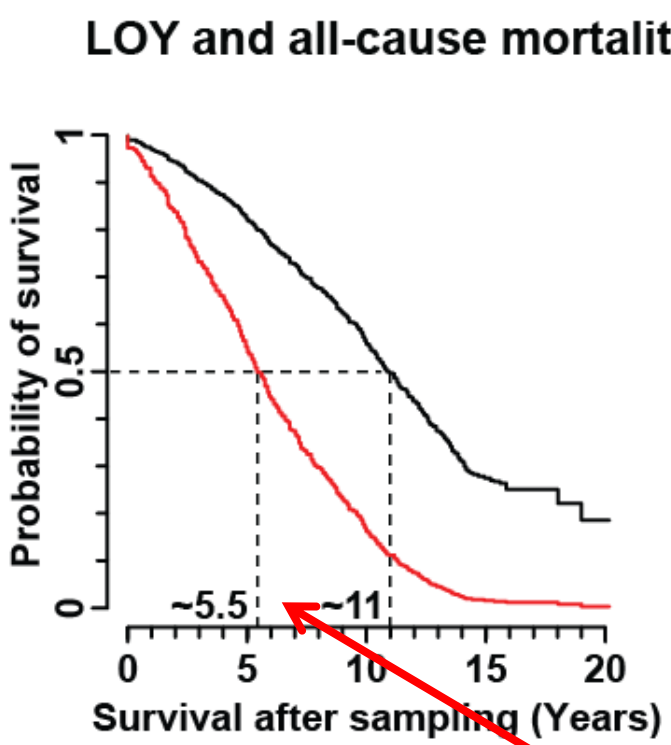
Lars A Forsberg[1,2], Chiara Rasi[1,2], Niklas Malmqvist[1–3], Hanna Davies[1,2], Saichand Pasupulati[1,2], Geeta Pakalapati[1,2], Johanna Sandgren[4], Teresita Diaz de Ståhl[4], Ammar Zaghlool[1,2], Vilmantas Giedraitis[5], Lars Lannfelt[5], Joannah Score[6], Nicholas C P Cross[6], Devin Absher[7], Eva Tiensuu Janson[3], Cecilia M Lindgren[8,9], Andrew P Morris[8], Erik Ingelsson[2,3], Lars Lind[3] & Jan P Dumanski[1,2]

Nature Genetics vol. 46 (2014)

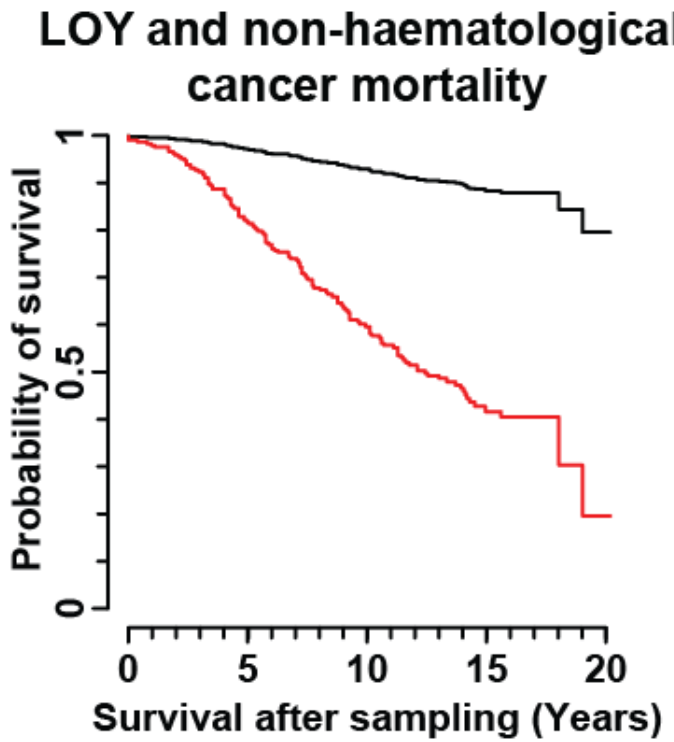
10 year anniversary of this discovery in April 2024!

LOY and mortality

GDAŃSKI UNIWERSYTET MEDYCZNY



HR=1.91 (95% CI 1.17-3.13)
No. events=637, p=0.010



HR=3.62 (95% CI 1.56-8.41)
No. events=132, p=0.003

Median survival among men with high degree of LOY was 5.5 years shorter

LOY in blood is associated with mortality and risk for many diseases

GDAŃSKI UNIWERSYTET MEDYCZNY

All-cause mortality and cancer
Forsberg et al. Nature Genetics 2014

Smoking causes LOY
Dumanski et al. Science 2015

Alzheimer's disease
Dumanski et al. Am J Hum Genet 2016

>710 citations

~180 papers reporting new data about LOY and its consequences (2015-2023)

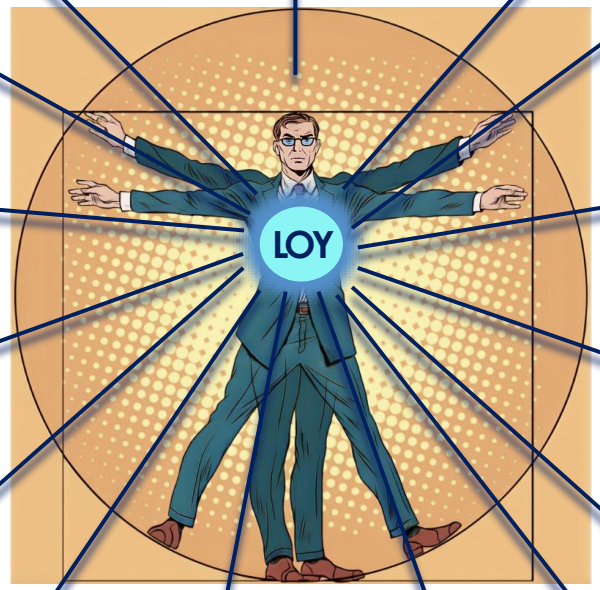
Myelodysplastic syndrome
Ganster et al. Genes Chr & Can 2015

Prostate and colorectal cancer
Noveski et al. PLOS One 2016

Prostate and bladder cancer
Zhou et al. Nature Genetics 2016

Testicular germ cell tumors
Machiela et al. J. Hu. Genet. 2017

Overall solid tumor incidence
Loftfield et al. Cancer Research 2019



Autoimmune conditions
Persani et al. 2012 and Lleo et al. 2013

Age-related macular degeneration
Grassman et al. EJHG 2018

Schizophrenia
Hirata et al. Neuro. Dis. Treat. 2018

Cardiovascular events
Haitjema et al. Circ. Card. Genet. 2017

Cardio-vascular disease, diabetes and all-cause mortality
Loftfield et al. Scientific Reports 2018

COVID-19
Bruhn-Olszewska et al. Genome Medicine 2022

Ischemic stroke
Dorvall et al. Stroke 2023

~180 papers in the literature reporting new data about LOY and its consequences (2015-2023)

GDAŃSKI UNIWERSYTET MEDYCZNY

10 of these are derived from us during the funding period from FNP

Thompson et al. Nature, 2019: **Genetic predisposition to LOY**

Danielsson et al. Eur J Hum Genet, 2020: **LOY is a dynamic mutation**

Dumanski et al. Cell Mol Life Sci, 2021: **LOY causes global deregulation of transcriptome**

Mattisson et al. Scientific Reports, 2021: **LOY affects permeability of blood vessels**

Bruhn-Olszewska et al. Genome Medicine, 2022: **LOY modulates the severity of COVID-19**

Ljungstrom et al. Leukemia, 36, 2022: **LOY & clonal hematopoesis**

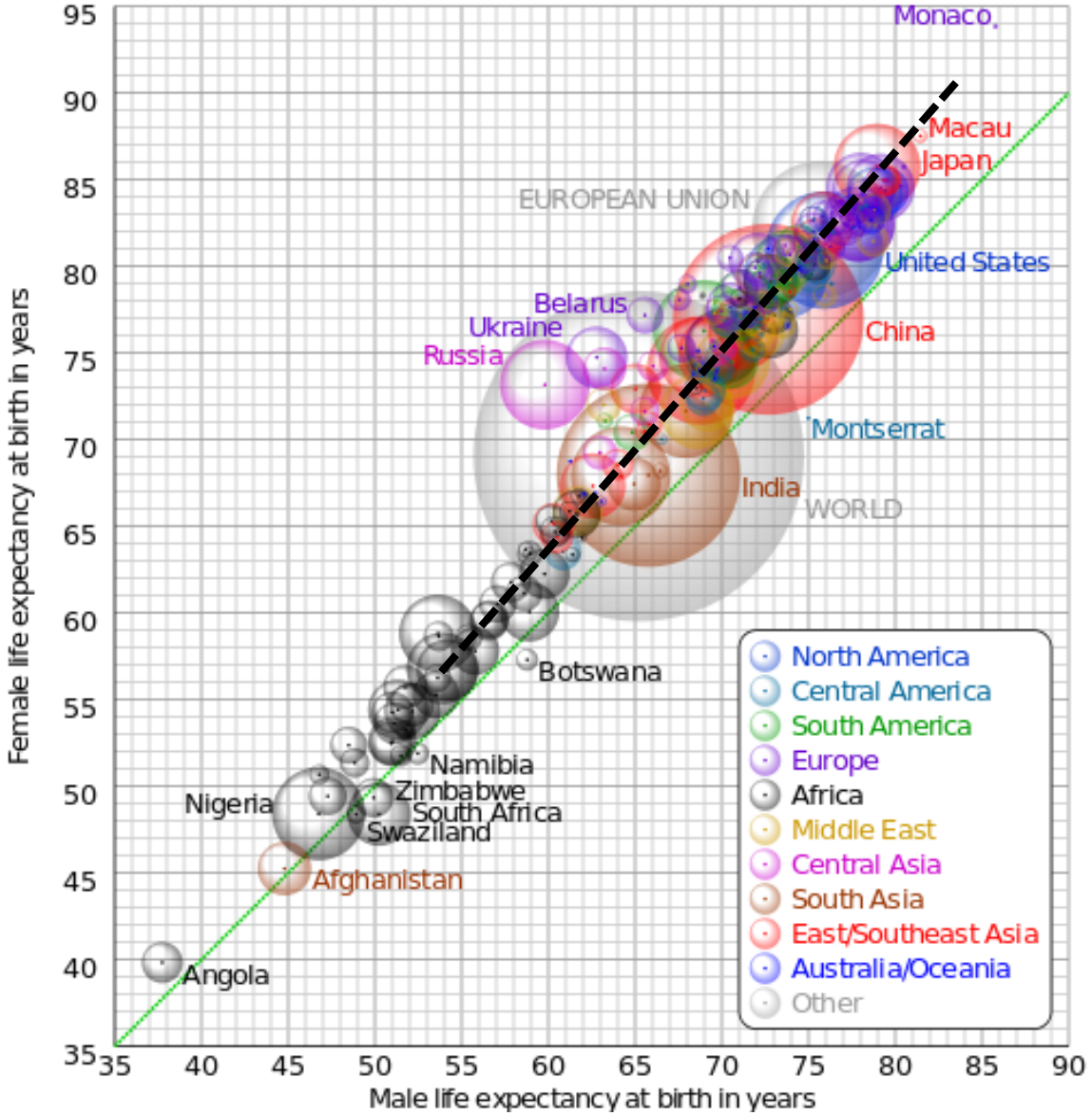
Dorvall et al. Stroke 2023: **LOY is associated with ischemic stroke**

Wójcik et al. Scientific Reports, in press, 2023: **LOY occurs in Tregs among cancer patients**

Mattisson et al. submitted, 2023: **LOY occurs in Tregs among cancer patients**

Jakalski et al. submitted, 2023: **LOY is associated with global DNA (CpG) methylation changes**

Males live shorter than females



Monaco ~9 years difference

Macau ~7 years difference

Japan ~6-7 years difference

EU ~6 years difference

USA ~5 years difference

Sweden ~5 years difference

The world ~4 years difference

What are the causes?

LOY might explain this!

Alterations in histologically normal breast tissue leading to sporadic breast cancers

GDAŃSKI UNIWERSYTET MEDYCZNY

Research

Signatures of post-zygotic structural genetic aberrations in the cells of histologically normal breast tissue that can predispose to sporadic breast cancer

Lars A. Forsberg,[1,12] Chiara Rasi,[1,12] Gyula Pekar,[1,2] Hanna Davies,[1] Arkadiusz Piotrowski,[3] Devin Absher,[4] Hamid Reza Razzaghian,[1,13] Aleksandra Ambicka,[5] Krzysztof Halaszka,[5] Marcin Przewoźnik,[5] Anna Kruczak,[5] Geeta Mandava,[1] Saichand Pasupulati,[1] Julia Hacker,[1,14] K. Reddy Prakash,[1] Ravi Chandra Dasari,[1] Joey Lau,[6,7] Nelly Penagos-Tafurt,[1] Helena M. Olofsson,[1] Gunilla Hallberg,[8] Piotr Skotnicki,[5] Jerzy Mituś,[5] Jaroslaw Skokowski,[9,10] Michal Jankowski,[11] Ewa Śrutek,[11] Wojciech Zegarski,[11] Eva Tiensuu Janson,[7] Janusz Ryś,[5] Tibor Tot,[1,2] and Jan P. Dumanski[1]

25:1521–1535 Published by Cold Spring Harbor Laboratory Press; ISSN 1088-9051/15; www.genome.org

Genome Research
www.genome.org

Genome Research 2015

RESEARCH ARTICLE

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

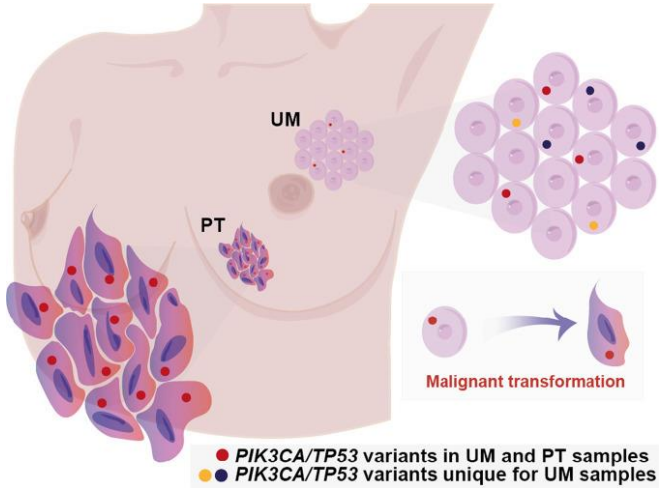
Concurrent DNA Copy-Number Alterations and Mutations in Genes Related to Maintenance of Genome Stability in Uninvolved Mammary Glandular Tissue from Breast Cancer Patients

Anna Ronowicz,[1†] Anna Janaszak-Jasiecka,[1†] Jarosław Skokowski,[2,3†] Piotr Madanecki,[1] Rafal Bartoszewski,[1] Magdalena Bałut,[1] Barbara Seroczyńska,[2] Kinga Kochan,[1] Adam Bogdan,[1] Małgorzata Butkus,[1] Rafał Pęksa,[4] Magdalena Ratajska,[5] Alina Kuźniacka,[5] Bartosz Wasąg,[5] Magdalena Gucwa,[1] Maciej Krzyżanowski,[6] Janusz Jaśkiewicz,[3] Zbigniew Jankowski,[6] Lars Forsberg,[7] J. Renata Ochocka,[1] Janusz Limon,[5] Michael R. Crowley,[8] Patrick G. Buckley,[9] Ludwine Messiaen,[10] Jan P. Dumanski,[7] and Arkadiusz Piotrowski[1*]

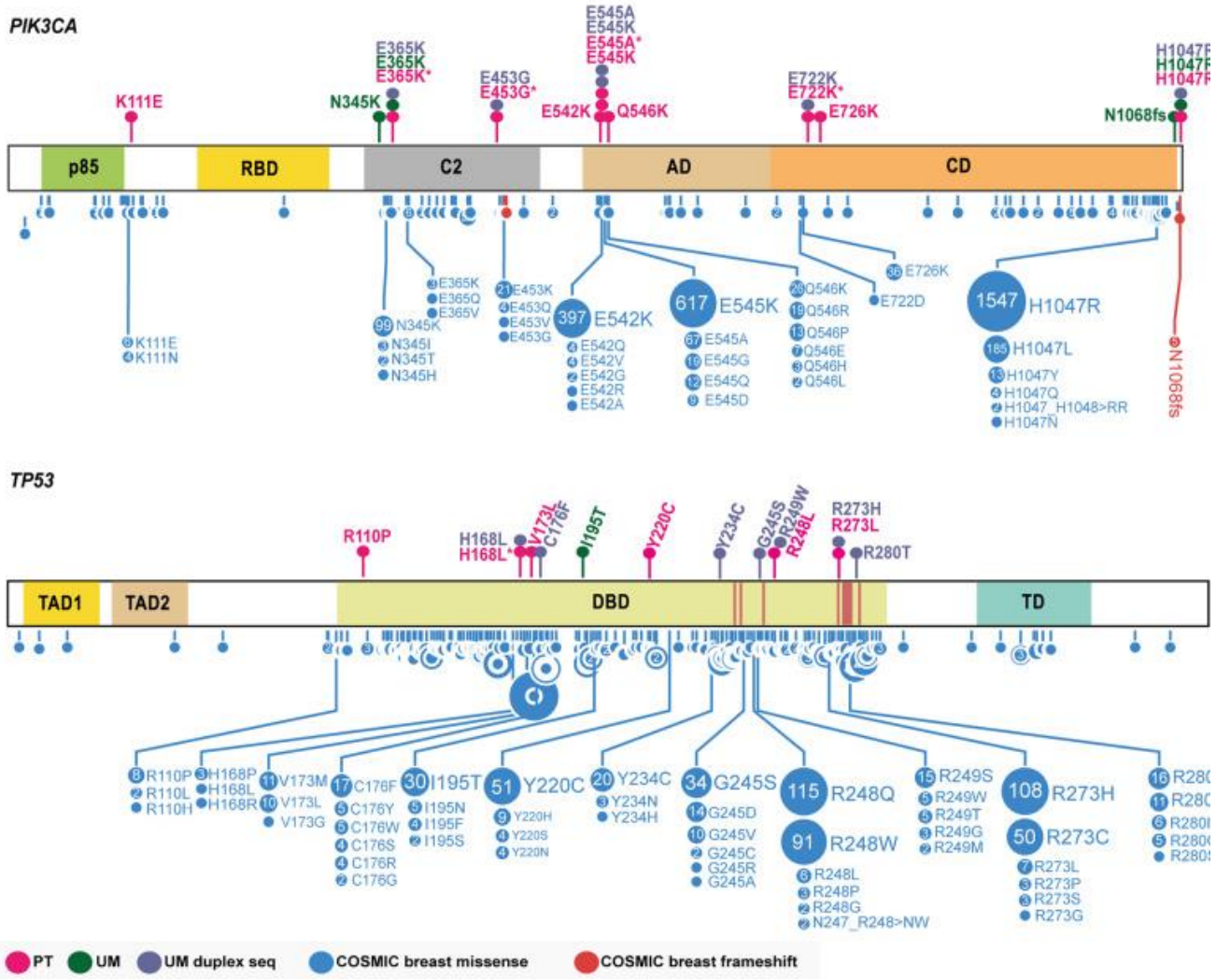
Human Mutations 2015

Somatic PIK3CA and TP53 variants in normal mammary gland cells of breast cancer patients

GDAŃSKI UNIWERSYTET MEDYCZNY



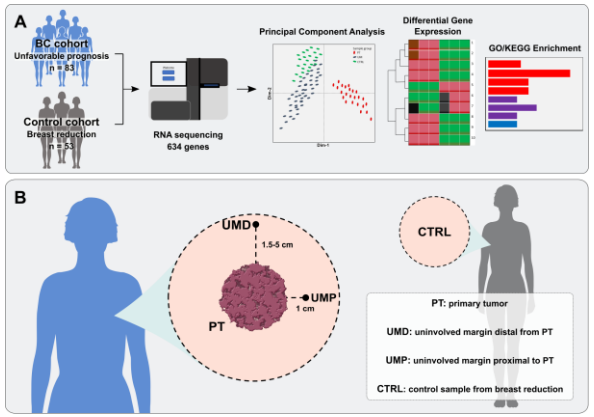
Chromosomal aberrations and pathogenic point variants in breast cancer driver genes are frequent in the normal mammary tissue **that remains after conservative surgery**

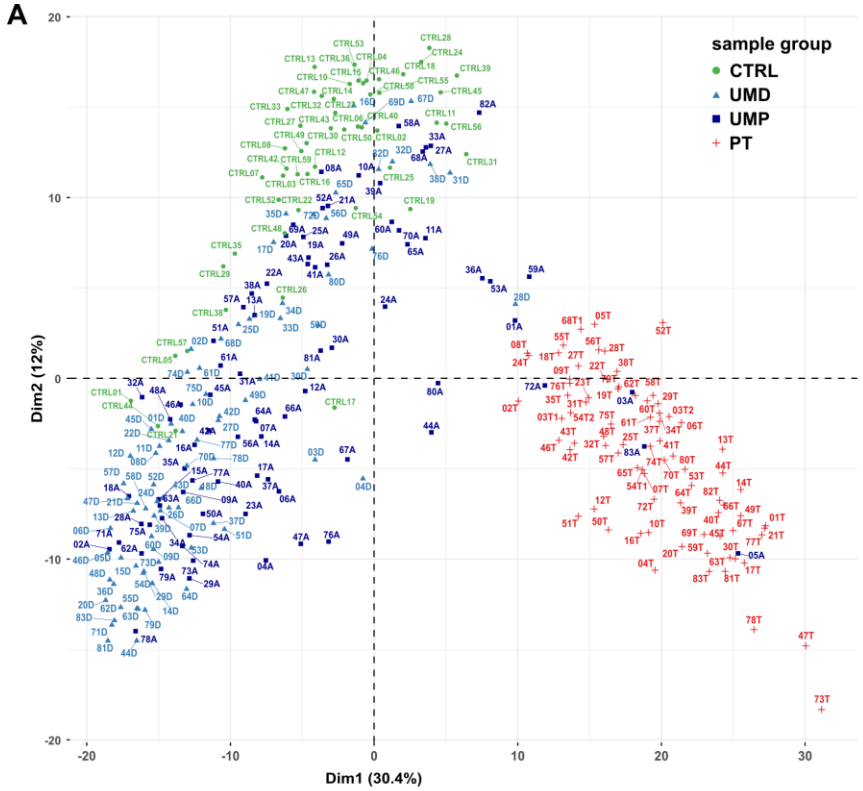


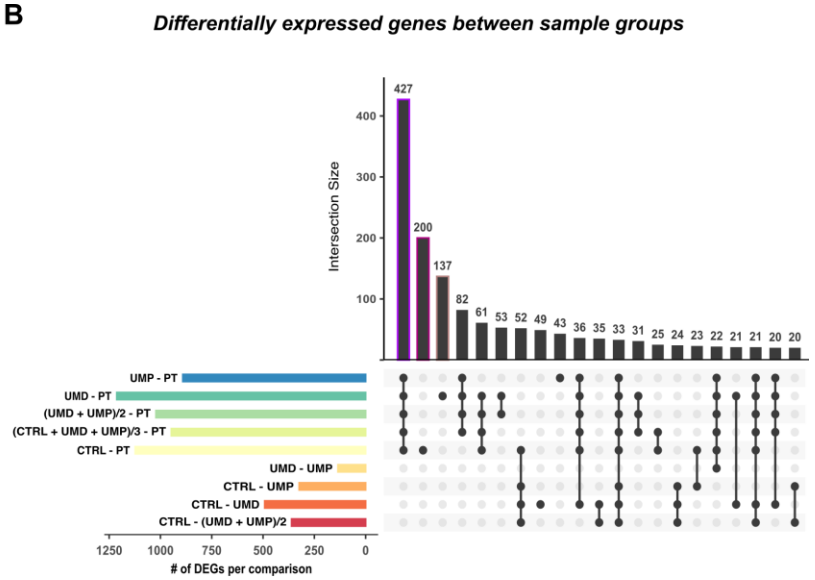
Kostecka *et al. 2022;* https://doi.org/10.1038/s41523-022-00443-9

A gene expression signature in normal mammary gland of breast cancer patients suggests pre-tumorous alterations

GDAŃSKI UNIWERSYTET MEDYCZNY





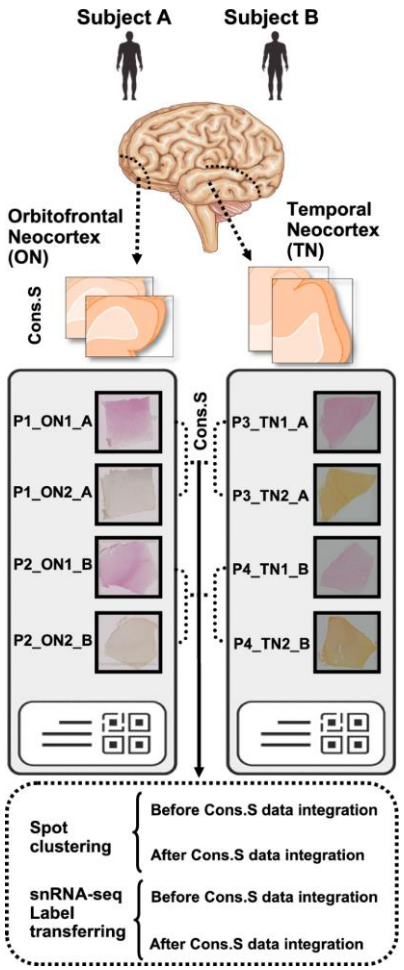


Pre-tumorigenic environment within normal mammary gland is associated with elevated mortality

A distinct gene expression signature identified in uninvolved mammary gland samples, featuring key cellular components

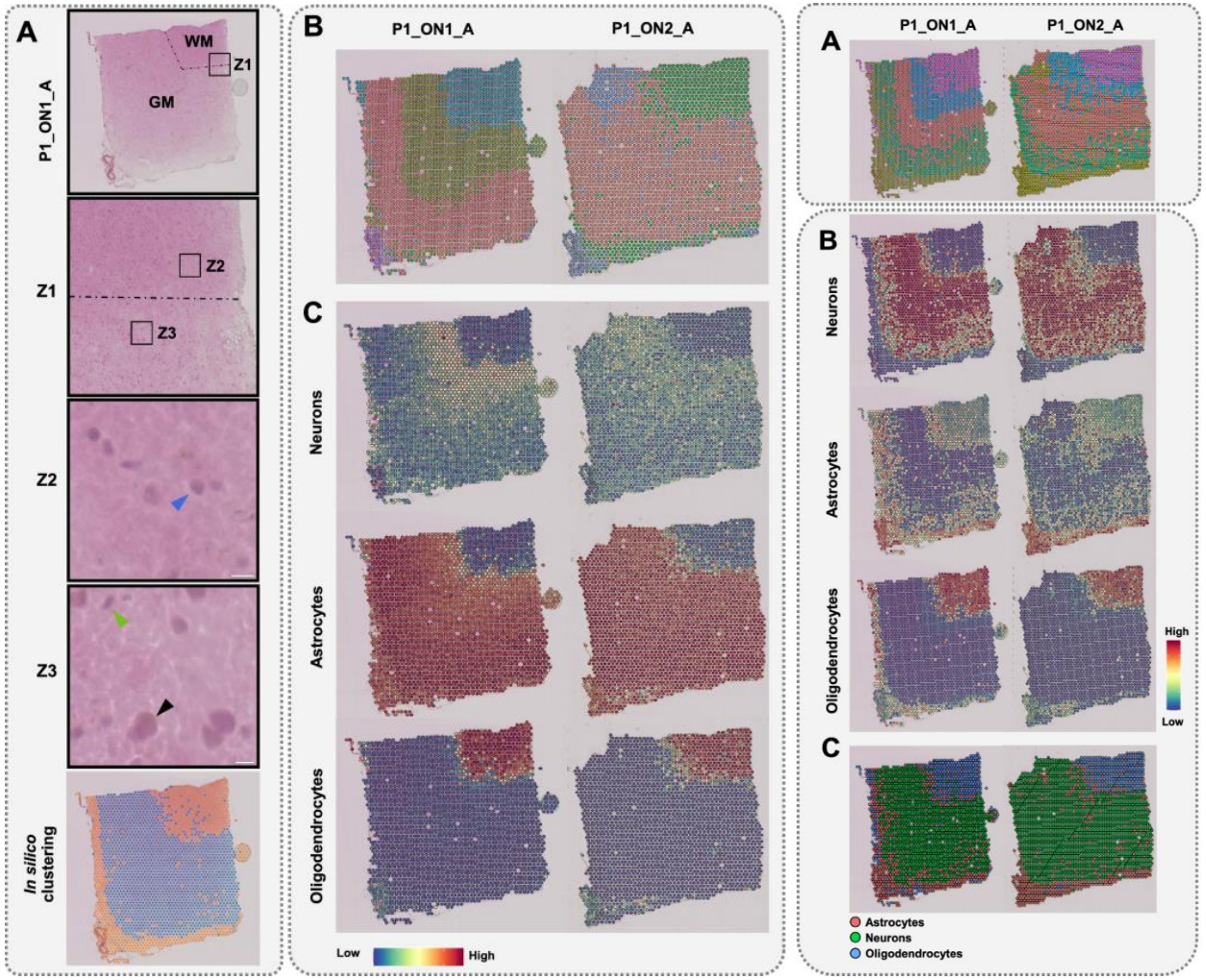
Andreou et al. 2023, submitted

Visium Spatial Gene Expression combining histological information with transcriptomic profile from human cerebral cortex



Consecutive Slices Data Integration can be applied to investigate serial sections:

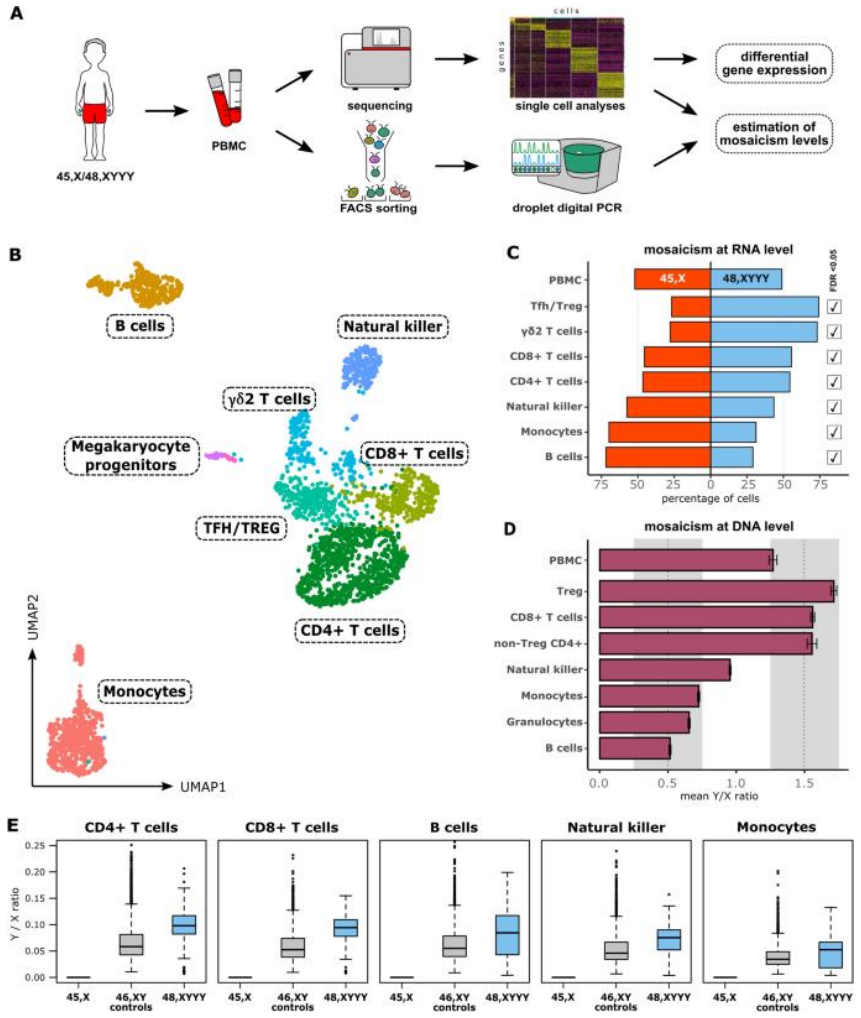
- avoiding misinterpretation of spot clustering
- increasing accuracy of cell recognition
- improving uncovering the layers of grey matter

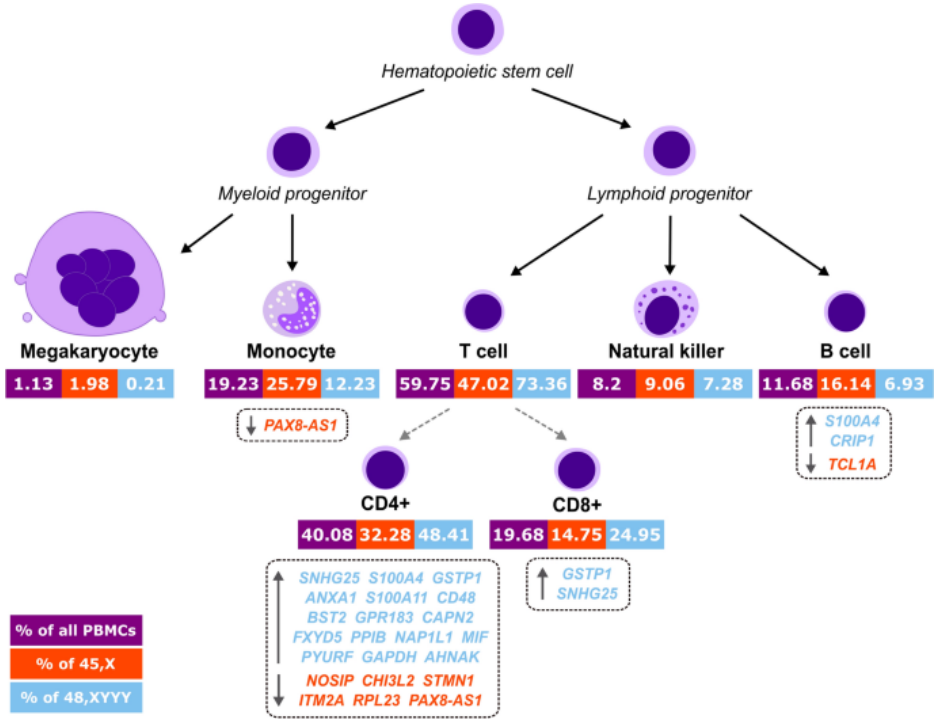


Mohammadi *et al. 2023;* https://doi.org/10.1186/s12967-023-04129-z

scRNA-seq combined with cell sorting and ddPCR in the analysis of a male with rare 45, X/48, XYYY karyotype

GDAŃSKI UNIWERSYTET MEDYCZNY



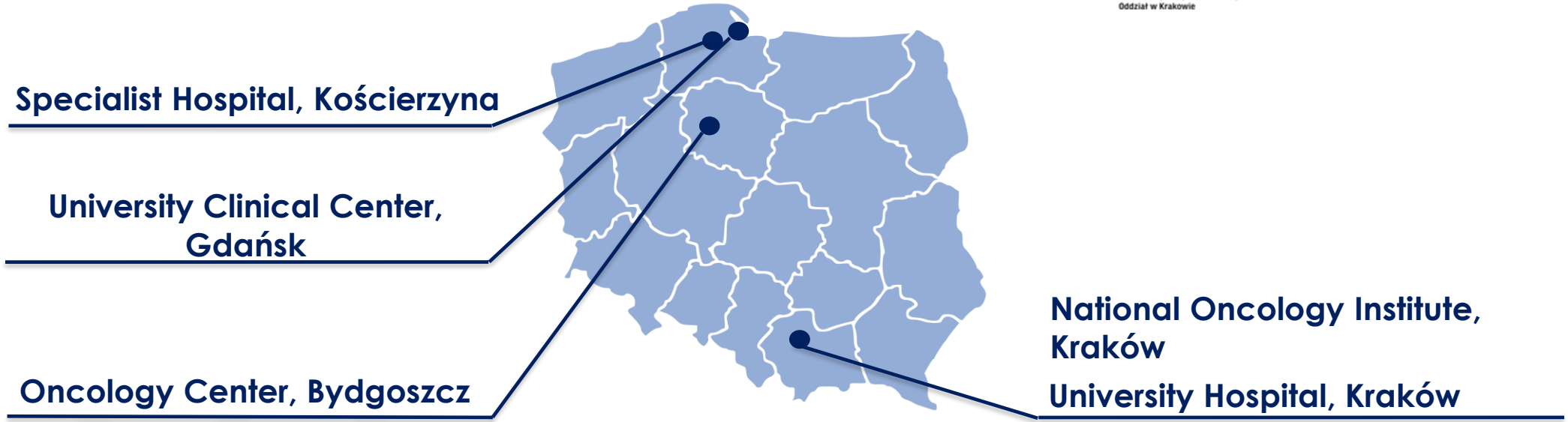


Synergistic effects and clinical utility of translational collaboration between the research laboratory and the clinic enabling genotype-driven personalized medicine

Koczkowska *et al. 2022;* https://doi.org/10.1038/s41598-022-25308-w

Biobanking collection for postzygotic variation studies

Szpital Specjalistyczny w Kościerzynie sp. z o.o.
Podmiot Leczniczy Samorządu Województwa Pomorskiego
UCK Uniwersyteckie Centrum Kliniczne
CENTRUM ONKOLOGII
Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie Państwowy Instytut Badawczy Oddział w Krakowie
Szpital Uniwersytecki w Krakowie
GDAŃSKI UNIWERSYTET MEDYCZNY



DONORS – ~4,300

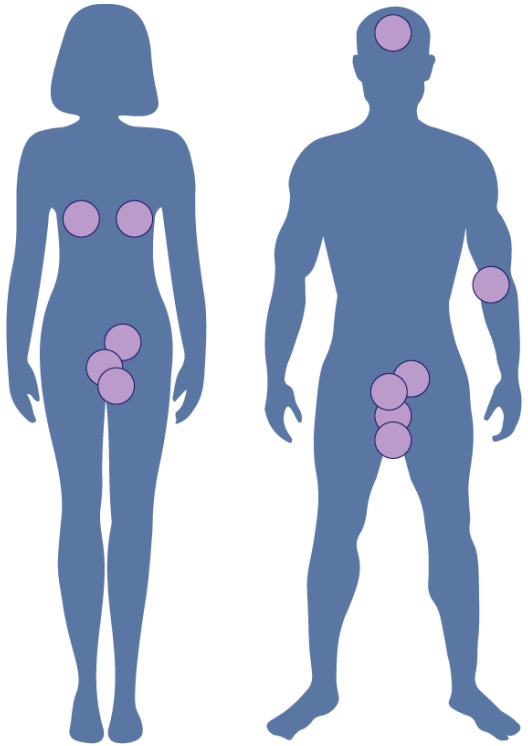
ORIGINAL SAMPLES – >45,000

ALL SAMPLES – >107,000

Biobanking collection for postzygotic variation studies

GDAŃSKI UNIWERSYTET MEDYCZNY

- Breast carcinoma - **1852**
- Colorectal carcinoma - **869**
- Prostate carcinoma - **592**
- Bladder carcinoma - **239**
- Kidney carcinoma - **241**
- Pancreas carcinoma - **42**



- Alzheimer Disease - **45**
- Healthy controls - **105**
- Mammoreduction controls - **32**

Other projects and retrospective collections - **~230**

LARGEST ONCOLOGICAL COLLECTION IN POLAND

Filipowicz *et al. 2022;* https://doi.org/10.1371/journal.pone.0266111

Acknowledgements:

- To all leaders, employees and students of 3P-Medicine Laboratory
- To members of Molecular Oncology group at Uppsala University
- To International Scientific Committee members under the leadership of Prof. Ulf Landegren (UU)
- To all clinical partners engaged in biobanking activities.

GDAŃSKI UNIWERSYTET MEDYCZNY

The End

Thank you for your attention

www.gumed.edu.pl